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In re Patent Application of:
Harold G. BROWN et al.

Examiner: F. C. Prats

Application No.: 09/890,425

Confirmation No.: 001812

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Art Unit: 1651

For: A PHARMACEUTICAL COMPOSITION OF COMPLEX CARBOHYDRATES AND ESSENTIAL OILS AND METHODS OF USING THE SAME

DECLARATION UNDER 37 CFR 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Karen K. Brown, B.S., Ph.D., do declare and say as follows:

1. I am a graduate of Washburn University, Topeka, Kansas and Oklahoma State University, Stillwater, Oklahoma.

2. My mailing address is c/o Dermal Research Laboratories, Inc., 5501 N.W. Foxhill Road, Parkville, Missouri 64152.

3. I am presently employed by Dermal Research Laboratories, Inc., in the position of Chief Technology Officer (Partner & Secretary).

4. I am listed as one of the inventors of the subject of the above-identified application. I have read and I understand the prosecution history of the present application.

5. For the research leading to the present application and at the time that the present application was prepared, Applicants based the molecular weight measurements on the protein standard rather than the dextran standard. The specific method used was size exclusion

chromatography (gel permeation chromatography or HPLC) and the protein standards were Immunoglobulin M, with a molecular weight of 900,000 daltons, Thyroglobulin with a molecular weight of 670,000 daltons, Gamma globulin with a molecular weight of 158,000 daltons and Ovalbumin with a molecular weight of 44,000 daltons. Using this method, one of the complex carbohydrates used by applicants as an example of an effective high molecular weight component was confirmed to have a molecular weight greater than 1,000,000 daltons by a third party laboratory, using the same protein standards (see attached document titled "Certificate of Analysis No. 030791).

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: January 19, 2007 By: _____

Karen K. Brown, Ph.D.
Chief Technology Officer (Partner & Secretary)
Dermal Research Laboratories, Inc.

Toxicity Profiles

Toxicity Summary for CHLOROFORM

NOTE: Although the toxicity values presented in these toxicity profiles were correct at the time they were produced, these values are subject to change. Users should always refer to the Toxicity Value Database for the current toxicity values.

Download a WordPerfect version of this toxicity profile. Please note that this document has been saved in WordPerfect 5.1/5.2 for greater accessibility but may have been originally formatted in later versions of WordPerfect (i.e., WordPerfect 6.1, Suite 7, etc.); therefore, formatting changes (i.e., Contents and Page Numbering) may occur when downloading this document.

DECEMBER 1992

Prepared by: Rosmarie A. Faust, Ph.D, Chemical Hazard Evaluation and Communication Group, Biomedical and Environmental Information Analysis Section, Health and Safety Research Division, *, Oak Ridge, Tennessee.

Prepared for: OAK RIDGE RESERVATION ENVIRONMENTAL RESTORATION PROGRAM.

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EXECUTIVE SUMMARY

Chloroform is a colorless, volatile liquid that is widely used as a general solvent and as an intermediate in the production of refrigerants, plastics, and pharmaceuticals (Torkelson and Rowe, 1976; IARC, 1976). Chloroform is rapidly absorbed from the lungs and the gastrointestinal tract, and to some extent through the skin. It is extensively metabolized in the body, with carbon dioxide as the major end product. The primary sites of metabolism are the liver and kidneys. Excretion of chloroform occurs primarily via the lungs, either as unchanged chloroform or as carbon dioxide (ATSDR, 1989).

Target organs for chloroform toxicity are the liver, kidneys, and central nervous system. Liver effects (hepatomegaly, fatty liver, and hepatitis) were observed in individuals occupationally exposed to chloroform (Bomski et al., 1967). Several subchronic and chronic studies by the oral or inhalation routes of exposure documented hepatotoxic effects in rats, mice, and dogs (Palmer et al., 1979; Munson et al., 1979; Heywood et al., 1979). Renal effects were reported in rats and mice following oral and inhalation exposures (Roe et al., 1979; Reuber, 1976; Torkelson et al., 1976), but evidence for chloroform-induced renal toxicity in humans is sparse. Chloroform is a central nervous system depressant, inducing narcosis and anesthesia at high concentrations. Lower concentrations may cause irritability, lassitude, depression, gastrointestinal symptoms, and frequent and burning urination (ATSDR, 1989).

Developmental toxicity studies with rodents indicate that inhaled and orally administered chloroform is toxic to dams and fetuses. Possible teratogenic effects were reported in rats and mice exposed to chloroform by inhalation (Schwetz et al., 1974; Murray et al., 1979). Chloroform may cause sperm abnormalities in mice and gonadal atrophy in rats (Palmer et al, 1979; Reuber, 1979; Land et al., 1981).

A Reference Dose (RfD) of 0.01 mg/kg/day for subchronic and chronic oral exposure was calculated from a lowest-observed-adverse-effect level (LOAEL) of 15 mg/kg/day based on fatty cyst formation in the liver of dogs exposed to chloroform for 7.5 years (Heywood et al., 1979). Development of an inhalation Reference Concentration (RfC) is presently under review (U.S. EPA, 1992b).

Epidemiological studies indicate a possible relationship between exposure to chloroform present in chlorinated drinking water and cancer of the bladder, large intestine, and rectum. Chloroform is one of several contaminants present in drinking water, but it has not been identified as the sole or primary cause of the excess cancer rate (ATSDR, 1989; U.S. EPA, 1985). In animal carcinogenicity studies, positive results included increased incidences of renal epithelial tumors

in male rats, hepatocellular carcinomas in male and female mice, and kidney tumors in male mice (Jorgensen et al., 1985; Roe et al., 1979; NCI, 1976).

Based on U.S. EPA guidelines, chloroform was assigned to weight-of-evidence Group B2, probable human carcinogen, on the basis of an increased incidence of several tumor types in rats and in three strains of mice. The carcinogen slope factor (q_1^*) for chloroform is 6.1E-3 $(mg/kg/day)^{-1}$ for oral exposure (U.S. EPA, 1992b) and 8.1E-2 $(ug/m^3)^{-1}$ for inhalation exposure (U.S. EPA, 1992a). An inhalation unit risk of 2.3E-5 $(g/m^3)^{-1}$ is based on hepatocellular carcinomas in mice in an oral gavage study (U.S. EPA, 1992b).

1. INTRODUCTION

Chloroform ($CHCl_3$; CAS No. 67-66-3), also known as trichloromethane, is a colorless, volatile liquid with a pleasant ethereal odor (DeShon, 1979; IARC, 1979). It has a molecular weight of 119.38, a density of 1.485 g/cm^3 at 20C (Hawley, 1981), and an octanol/water partition coefficient of 1.97 (Hansch and Leo, 1985). It is only slightly soluble in water, but is miscible with alcohol, benzene, ether, petroleum ether, carbon tetrachloride, carbon disulfide, and oils (Budavari et al., 1989). Chloroform is widely used as an intermediate in the production of refrigerants, plastics, and pharmaceuticals, and as a general solvent or constituent of solvent mixtures (Torkelson and Rowe, 1981; IARC, 1979). In the past, chloroform has been extensively used as a surgical anesthetic, but this use was discontinued because exposure to narcotic concentrations resulted in adverse side effects. The Food and Drug Administration has banned the use of chloroform as an ingredient in human drug and cosmetic products as of July, 1976 (U.S. FDA, 1976).

Human exposure to chloroform can occur orally, dermally, or by inhalation. Chloroform is the principal trihalomethane generated as by-products during the chlorination of drinking water. The primary sources of chloroform in the environment are chlorinated drinking water and wastewater, pulp and paper mills, and chemical and pharmaceutical manufacturing plants. Most of the chloroform released to the environment eventually enters the atmosphere, while much smaller amounts enter groundwater as a result of filtration through the soil (ATSDR, 1989).

2. METABOLISM AND DISPOSITION

2.1. ABSORPTION

Chloroform is rapidly absorbed through the lungs and the gastrointestinal tract, and to some extent through the skin (Torkelson and Rowe, 1981). In humans, the respiratory absorption of chloroform ranges from 49 to 77% (ATSDR, 1989) and absorption from the gastrointestinal tract approximates 100%, with peak blood levels being reached within 1 hour (Fry et al., 1972). Essentially complete oral

absorption has also been reported in rats, mice, and monkeys (Brown et al., 1974; Taylor et al., 1974).

2.2. DISTRIBUTION

Following its absorption, chloroform is distributed to all organs (IARC, 1979). Humans exposed to chloroform by inhalation exhibited a three-component decrease of blood chloroform levels, with a rapid phase having a half-life of 14 min, a slower phase with a half-life of 90 min, and a very slow phase with an undetermined half-life (Fry et al., 1972). A number of studies have shown that chloroform accumulates in the body fat of humans and animals. It is lipid soluble, readily passes through cell membranes, reaching relatively high concentrations in nervous tissue. Chloroform concentrations in tissues are dose-related and occur in the following order: adipose > brain > liver > kidney > blood (ATSDR, 1989). Chloroform passes through the placenta and has been detected in fetal blood at levels equal to or greater than those in maternal blood (Dowty et al., 1976).

2.3. METABOLISM

Chloroform is metabolized by oxidative dehydrochlorination of its carbon-hydrogen bond to form phosgene (CCl_2O). The reaction is P450-mediated and occurs in both the liver and the kidney. The major end product of chloroform metabolism is carbon dioxide (CO_2), most of which is eliminated via the lungs, but some is incorporated into endogenous metabolites and may be excreted as bicarbonate, urea, methionine and other amino acids, inorganic chloride ion, and carbon monoxide (ATSDR, 1989).

2.4. EXCRETION

Fry et al. (1972) studied a group of volunteers who ingested 500 mg of ^{14}C-labelled chloroform. More than 96% of the administered isotope was exhaled within 8 hours, 18-67% of which was excreted unchanged by this route; less than 1% appeared in urine. Lean subjects eliminated a greater percentage of the dose via the lungs than overweight subjects. The fraction reported metabolized to CO_2 was 46% for a male and 58% for a female (Fry et al., 1972; Chiou, 1975). Rats, mice, and monkeys excreted 6, 20, and 78%, respectively, of an oral 60-mg/kg dose as unchanged parent compound in air (Torkelson and Rowe, 1981).

3. NONCARCINOGENIC HEALTH EFFECTS

3.1. ORAL EXPOSURES

3.1.1. Acute Toxicity

3.1.1.1. Human

Chloroform is acutely toxic to the liver although damage may not be fully apparent until 12-48 hours after exposure. Liver effects include centrilobular necrosis and reduced prothrombin formation (ATSDR, 1989). Schroeder (1965) reported that a fatal oral dose of chloroform may be as little as 10 mL (14.8 g), with death due to respiratory or cardiac arrest. Gosselin et al. (1984) estimate that the mean lethal oral dose is 44 g for humans.

3.1.1.2. Animal

Oral LD_{50} values range from 444 to 2000 mg/kg for rats and from 118 to 1400 mg/kg for mice (U.S. Air Force, 1989). Torkelson et al. (1976) reported that 250 mg/kg of orally administered chloroform produced fatty infiltration and necrosis of the liver as well as kidney damage in rats. Liver and kidney damage was also reported in CD-1 mice treated daily for 14 days with 148 mg/kg chloroform in corn oil by gavage (Condie et al., 1983).

3.1.2. Subchronic Toxicity

3.1.2.1. Human

The long-term use of a dentrifice containing 3-4% chloroform and a mouthwash containing 0.43% chloroform was investigated in a study involving 299 subjects (DeSalva et al., 1975). Ingestion was estimated to be 0.3-0.96 mg/kg/day over a 1- to 5-year period. There were no statistical differences between experimental and control subjects in any of the parameters [alanine aminotransferase (ALT), aspartate aminotransferase (AST), and blood urea nitrogen] monitored as tests for liver and kidney function.

3.1.2.2. Animal

Chu et al. (1982) exposed Sprague-Dawley rats to 5, 50, 500, or 2500 ppm chloroform in drinking water for 90 days. Increased mortality, decreased growth rate, and decreased food intake were reported at the highest dose. Histological examination of treated animals showed mild to moderate fatty infiltration of the liver and reduction in follicular size and colloid density of the thyroid. These lesions were not significantly different from controls, with the exception of thyroid effects observed in the highest-dosed males.

Chloroform administered by gavage in toothpaste at a dose of 15, 30, 150, or 410 mg/kg/day, 6 days/week for 13 weeks to Sprague-Dawley rats produced increased liver weight and fatty changes with necrosis in the high-dose group. Increased liver weights were seen at 150 mg/kg/day, but no effects were seen at the lower doses (Palmer et al., 1979).

Munson et al. (1982) administered 0, 50, 125, or 250 mg/kg/day chloroform by gavage to male and female CD-1 mice for 90 days. Chloroform-treated male and female mice exhibited increased liver weights and slight histologic changes in liver and kidneys.

Liver effects were also observed in beagle dogs administered chloroform in gelatin capsules at doses ranging from 30 to 120 mg/kg/day for up to 18 weeks (Heywood et al., 1979). At >= 60 mg/kg/day, hepatocyte enlargement with vacuolization, fatty deposits of the liver, and increased ALT, AST, and serum alkaline phosphatase (SAP) activity were observed.

3.1.3. Chronic Toxicity

3.1.3.1. Human

Hepatitis and kidney nephrosis were reported in a patient who had ingested a chloroform-containing cough-suppressant over a ten-year period. Chloroform intake was estimated at 1.6-2.6 g/day (Wallace, 1950). Although the investigator attributed the effects to chloroform, the patient had ingested moderate amounts of alcohol daily, a known liver toxicant, until about a year prior to the examination.

3.1.3.2. Animal

Palmer et al. (1979) administered 3.5% chloroform in toothpaste by gavage for 80 weeks to male and female Sprague-Dawley rats. Retardation in weight gain and decreases in relative liver weights were observed in female rats. Decreased plasma cholinesterase activity was observed in both sexes.

Reuber (1979) re-examined histological sections from an NCI (1976) carcinogenesis bioassay in which rats received 90 mg/kg/day chloroform by gavage for 78 weeks. Interstitial fibrosis of the kidneys, polyarteritis of the mesenteric, pancreatic, and other arteries, and testicular atrophy were observed in rats receiving this dose.

Roe et al. (1979) administered chloroform in toothpaste, by gavage, to mice at doses of 0, 17, or 60 mg/kg/day, 6 days/week for 80 weeks, followed by 16-24 weeks of observation. There was an increased incidence of moderate to severe renal disease and benign and malignant tumors in the group treated with 60 mg/kg/day. No adverse effects occurred in the lower-dose group.

Male and female beagle dogs were fed capsules containing 0, 15, or 30 mg/kg/day chloroform in a toothpaste base, 6 days/week for 7.5 years, followed by 20 to 24 weeks of observation (Heywood et al., 1979). Fatty cysts were found in the liver of all groups; however, they were larger and more numerous in chloroform-treated dogs. There was also a moderate dose-related increase in serum ALT activity and other serum enzymes, indicative of liver damage

3.1.4. Developmental and Reproductive Toxicity

3.1.4.1. Human

Information on the developmental and reproductive toxicity of chloroform following oral exposure in humans was unavailable.

3.1.4.2. Animal

Thompson et al. (1974) orally administered chloroform to rats (20, 50, or 126 mg/kg/day) and rabbits (20, 35, or 50 mg/kg/day) on gestation days 6-15 and 6-18, respectively. In rats, no adverse effects occurred at 20 mg/kg/day, but maternal toxicity, characterized by decreased body weight gain and mild fatty change in the liver, was evident at >= 50 mg/kg. Fetal body weights were significantly decreased at 126 mg/kg/day. In rabbits, maternal weight gain was decreased at 50 mg/kg, and mean fetal body weight was decreased at 20 and 50 mg/kg/day, but not at 35 mg/kg/day.

Testicular atrophy was one of the effects observed in SD rats administered chloroform at a dose of 410 mg/kg/day by gavage for 13 weeks (Palmer et al., 1979) and in Osborne-Mendel rats administered 90 mg/kg/day by gavage for 78 weeks (Reuber, 1979).

3.1.5. Reference Dose

3.1.5.1. Subchronic

- ORAL RfD: 0.01 mg/kg/day (U.S. EPA, 1992a,b)
- UNCERTAINTY FACTOR: 1000
- LOAEL: 15 mg/kg/day
- COMMENT: The same study applies to the subchronic and chronic RfD. The study is described in Section 3.1.3.2.

3.1.5.2. Chronic

- ORAL RfD: 0.01 mg/kg/day (U.S. EPA, 1992a,b)
- UNCERTAINTY FACTOR: 1000
- LOAEL: 15 mg/kg/day
- CONFIDENCE:
  Study: Medium
  Data Base: Medium
  RfD: Medium
- VERIFICATION DATE: 12/02/85
- PRINCIPAL STUDY: Heywood et al., 1979
- COMMENTS: The LOAEL was based on the formation of fatty cysts in the liver of dogs. The uncertainty factor of 1000 includes a factor of 10 for

interspecies extrapolation, 10 for protection of sensitive human subpopulations, and 10 for extrapolation from LOAEL to NOAEL (U.S. EPA, 1992b).

3.2. INHALATION EXPOSURES

3.2.1. Acute Toxicity

3.2.1.1. Human

Chloroform is a central nervous system (CNS) depressant. Concentrations of 20,000 to 40,000 ppm were formerly used to induce anesthesia with lower concentrations used to maintain it. Delayed toxic effects observed after use as an anesthetic included drowsiness, restlessness, vomiting, fever, elevated pulse rate, jaundice, liver enlargement, abdominal tenderness, abnormal liver and kidney function, delirium, and coma. Chloroform may sensitize the heart to epinephrine, causing arrhythmias (ATSDR, 1989). In experimental human exposures to chloroform vapors, approximately 14,000-16,000 ppm caused narcosis. Dizziness, intracranial pressure, and nausea resulted after a 7-minute exposure to 1000 ppm, with fatigue and headache as after effects. A 30-minute exposure to 390 ppm caused no adverse effects (Torkelson and Rowe, 1981).

3.2.1.2. Animal

An inhalation LC_{50} of 10,000 ppm for rats exposed to chloroform for 4 hours was reported by Lundberg et al. (1986). Exposure to 2500 ppm for 2 hours caused no obvious CNS effects in mice; 3100 ppm for 1 hour induced slight narcosis; and 4000 ppm induced deep narcosis within 30 minutes. Cats exposed to 7200 ppm experienced disturbed equilibrium after 5 minutes and narcosis as exposure duration increased (U.S. EPA, 1985).

3.2.2. Subchronic Toxicity

3.2.2.1. Human

Nine of ten female individuals occupationally exposed for approximately 5 years to chloroform vapors at an average breathing zone concentration of 128 ppm experienced various symptoms, including irritability, lassitude, depression, gastrointestinal distress, and frequent and burning urination (Challen et al., 1958). Workers exposed to lower concentrations and shorter time periods experienced less severe symptoms. No evidence of liver injury was seen in either exposure group.

Workers at a pharmaceutical plant, where chloroform was used as the main solvent, were exposed to an estimated air concentration of 2-205 ppm of chloroform as well as to small amounts of other solvents (Bomski et al., 1967).

Enlarged livers were seen in 17/68 workers exposed regularly to chloroform for 1-4 years and still in contact with chloroform; in 5/39 workers with past exposure to chloroform; in 2/23 with hepatitis but no exposure to chloroform (positive controls); and in 2/164 workers with no hepatitis and no exposure to chloroform. Of the 17 workers still exposed who had enlarged livers, 4 had toxic hepatitis (based on increased alanine aminotransferase, aspartate aminotransferase, and serum gamma globulin levels) and 14 had fatty degeneration of the liver. Also reported was a high incidence of enlargement of the spleen as well as complaints of headache, nausea, eructation, and loss of appetite.

3.2.2.2. Animal

Torkelson et al. (1976) exposed rats, rabbits, and guinea pigs to 0, 25, 50, or 85 ppm chloroform vapor, 7 hours/day, 5 days/week for 6 months. Dogs (1/sex) were similarly exposed to 25 ppm. Increased relative kidney weights, cloudy swelling of the renal tubular epithelium, and lobular, granular degeneration with necrosis of the liver were seen in male rats at all three exposure concentrations. Also seen in male rats were decreased body weights at 50 and 85 ppm, and increased relative liver weights at 85 ppm. In female rats at 25 ppm, there was only an increase in relative kidney weights. At 50 and 85 ppm, liver and kidney pathology was similar to that seen in males. Experiments with rabbits and guinea pigs gave inconsistent results. Histological lesions were observed in the liver and kidneys of rabbits and guinea pigs at 25 ppm but not at 50 ppm in either species. At 85 ppm, histological lesions were observed in rabbits but not in guinea pigs. Histological changes in the kidneys were seen in the female but not the male dog at 25 ppm.

3.2.3. Chronic Toxicity

Information on the chronic inhalation toxicity of chloroform in humans or animals was unavailable.

3.2.4. Developmental and Reproductive Toxicity

3.2.4.1. Human

Information on the developmental and reproductive toxicity of chloroform following inhalation exposure in humans was unavailable.

3.2.4.2. Animal

Schwetz et al. (1974) exposed Sprague-Dawley rats to chloroform at concentrations of 0, 30, 100, or 300 ppm, 7 hours/day, on days 6-15 of gestation. Exposure to 30 ppm caused significantly increased incidences of fetal abnormalities, such as delayed skull ossification and wavy ribs compared with controls. At 100 ppm, there was a significantly increased incidence of missing

ribs, short or missing tail, imperforate anus, subcutaneous edema, and delayed ossification of sternebrae. A decrease in pregnancy rate, number of live fetuses/litter, and an increased percentage of litters with absorptions was seen at 300 ppm. Subcutaneous edema and skull abnormalities were also observed, but their incidence was not statistically significant, possibly due to the small number of surviving fetuses. Decreased maternal weight gain occurred at all dose levels.

Murray et al. (1979) observed an increased incidence of cleft palate, decreased fetal body weight, and decreased crown to rump length in CF-1 mice exposed to 100 ppm on days 8-15 of gestation.

Male mice exposed to 0.04 or 0.08% (400 or 800 ppm) chloroform, 4 hours/day for 5 days exhibited a significant increase in the percentage of abnormal sperm (Land et al., 1981).

3.2.5. Reference Concentration/Dose

A subchronic or chronic reference concentration/dose for chloroform was not available at this time. However, a risk assessment for chloroform is under review by an EPA work group (U.S. EPA, 1992b).

3.3. OTHER ROUTES OF EXPOSURE

3.3.1. Acute Toxicity

3.3.1.1. Human

Liquid chloroform in the eye causes tearing and conjunctivitis (Grant, 1974).

3.3.1.2. Animal

Dermal applications of 1000 mg/kg for 24 hours caused degenerative changes in kidney tubules of rabbits (Torkelson et al., 1976).

3.3.2. Subchronic Toxicity

Information on the subchronic toxicity of chloroform by other routes of exposure in humans or animals was unavailable.

3.3.3. Chronic Toxicity

Information on the chronic toxicity of chloroform by other routes of exposure in humans or animals was unavailable.

3.3.4. Developmental and Reproductive Toxicity

Information on the developmental and reproductive toxicity of chloroform by other routes of exposure in humans or animals was unavailable.

3.4. TARGET ORGANS/CRITICAL EFFECTS

3.4.1. Oral Exposures

3.4.1.1. Primary Target Organs

1. Liver: Following oral exposure to chloroform, hepatic effects in experimental animals include increased liver weight, fatty degeneration with necrosis of the liver, and increased liver enzyme activity. Hepatotoxic effects were reported in a patient who had ingested a chloroform-containing cough remedy over a 10-year period.
2. Kidney: Oral exposure to chloroform caused interstitial fibrosis in rats and necrosis, fibrosis, tubular degeneration, and hyperplasia in mice. Nephrosis was reported in a patient who had ingested chloroform in a cough remedy over a 10-year period.
3. Testes: After oral exposure to chloroform, rats exhibited testicular atrophy.

3.4.1.2. Other Target Organs

1. Thyroid: Reduction of follicular size and colloid density of the thyroid was reported in one study with rats.
2. Vascular system: Polyarteritis of mesenteric, pancreatic, and other arteries was reported in one study with rats.

3.4.2. Inhalation Exposures

3.4.2.1. Primary Target Organs

1. Liver: Following inhalation exposure to chloroform, hepatic effects in experimental animals included increased liver weights, lobular degeneration, and necrosis of the liver. Increased liver weights, fatty degeneration of the liver, and hepatitis were reported in individuals occupationally exposed to chloroform.
2. Kidney: Animals exposed to chloroform by inhalation developed increased kidney weights and cloudy swelling of the renal tubular epithelium.
3. Central nervous system: Symptoms in workers exposed to chloroform included headache, depression, irritability, and lassitude.
4. Gastrointestinal tract: Symptoms in workers exposed to chloroform included nausea, eructation, and lack of appetite.
5. Reproduction and development: After inhalation exposure to chloroform, reproductive effects in rats include decreased number of live fetuses/litter and increased resorptions. Also reported were missing ribs, short or missing tail, imperforate anus, subcutaneous edema, delayed ossification

of sternebrae, and skull abnormalities. An increased incidence of cleft palate and abnormal sperm as well as decreased fetal body weight was seen in mice.

3.4.2.2. Other Target Organs

Enlargement of the spleen was reported in humans occupationally exposed to chloroform.

4. CARCINOGENICITY

4.1. ORAL EXPOSURES

4.1.1. Human

Several epidemiological and case control studies of populations consuming chlorinated drinking water, containing chloroform as well as numerous other contaminants, showed small but significant increases in the incidence of cancer of the large intestine, rectum, and/or bladder. However, chloroform was not identified as the sole or primary cause for excess cancer (ATSDR, 1989). According to U.S. EPA (1985), the human data suggest a possible increased risk of cancer at these three sites because chloroform is the predominant trihalomethane in drinking water, but the data are too weak to draw a conclusion about the carcinogenic potential of chloroform.

4.1.2. Animal

In a carcinogenesis bioassay (NCI, 1976), Osborne-Mendel rats and B6C3F$_1$ mice were treated by gavage with chloroform in corn oil 5 times/week for 78 weeks. Male rats received 90 or 125 mg/kg/day; females were treated initially with 125 or 250 mg/kg/day for 22 weeks, and then with 90 or 180 mg/kg/day thereafter. Male and female mice initially received 100 or 200 mg/kg/day and 200 or 400 mg/kg/day, respectively. These levels were increased after 18 weeks to 150 or 300 and 250 or 500 mg/kg/day, respectively. In male rats, there was a significant dose-related increase in the incidence of kidney epithelial tumors; in male and female mice, there was a significant dose-related increase of hepatocellular carcinomas.

Jorgensen et al. (1985) administered 0, 200, 400, 900, or 1800 ppm chloroform (pesticide quality and distilled) in drinking water to male Osborne-Mendel rats and female B6C3F$_1$ mice for 104 weeks. In male rats, there was a significant ($p < 0.01$), dose-related increase in the incidence of renal tubular cell adenomas and/or adenocarcinomas that was slightly lower than that seen in the NCI (1976) study. However, in contrast to the NCI (1976) study, there was no increased incidence of hepatocellular tumors in female mice.

Roe et al. (1979) administered toothpaste containing chloroform (60 mg/kg/day, 6 days/week for 80 weeks, by gavage) to four strains of male mice. The incidence of kidney tumors was not increased in treated C57BL, CBA, or CF/1 mice. However, benign and malignant kidney tumors were seen in ICI mice.

According to IARC (1979), there is sufficient evidence that chloroform is carcinogenic in animals.

4.2. INHALATION EXPOSURES

Information on the carcinogenicity of chloroform following inhalation exposure in humans or animals was unavailable.

4.3. OTHER ROUTES OF EXPOSURE

U.S. EPA (1992b) reported negative results in pulmonary tumor bioassays in which two strains of mice were treated subcutaneously with chloroform.

4.4. EPA WEIGHT-OF-EVIDENCE

4.4.1. Oral

Classification -- B2; probable human carcinogen

Basis -- Increased incidence of several tumor types in rats and three strains of mice (U.S. EPA, 1992b).

4.4.2. Inhalation

Not assigned

4.5. CARCINOGENICITY SLOPE FACTORS

4.5.1. Oral

- SLOPE FACTOR: 6.1E-3 $(mg/kg/day)^{-1}$
- DRINKING WATER UNIT RISK: 1.7E-7 $(g/L)^{-1}$
- PRINCIPAL STUDY: Jorgensen et al. (1985)
- VERIFICATION DATE: 08/26/87 (U.S. EPA, 1992b)

4.5.2. Inhalation

- SLOPE FACTOR: 8.1E-2 $(g/m^3)^{-1}$ (U.S. EPA, 1992a)
- INHALATION UNIT RISK: 2.3E-5 $(g/m^3)^{-1}$ (U.S. EPA, 1992b)

- VERIFICATION DATE: 08/26/87
- PRINCIPAL STUDY: NCI, 1976
- COMMENT: The inhalation slope factor and unit risk were derived from an oral gavage study with mice (NCI, 1976).

5. REFERENCES

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Last Updated 8/29/97

Safety (MSDS) data for cetylpyridinium chloride

General

Synonyms: 1-palmitylpyridinium chloride, C16-alkylpyridinium chloride, 1-hexadecylpyridinium chloride, acetoquat CPC, aktivex, ammonyx CPC, cecure, ceepryn chloride, cepacol, ceprim, cepacol chloride, cetafilm, cetamium, dobendan, halset, ipanol, medilave, mercocet, merothol, pionin B, pristacin, pyrisept, further trade names
Use: sometimes used as an ingredient in pesticides.
Molecular formula: $C_{21}H_{38}ClN$
CAS No: 123-03-5
EC No: 204-593-9

Physical data

Appearance: white powder or crystals with a pyridine-like odour
Melting point: 77 C
Boiling point:
Vapour density:
Vapour pressure:
Specific gravity:
Flash point:
Explosion limits:
Autoignition temperature:

Stability

Stable. Combustible. Incompatible with strong oxidizing agents, strong bases.

Toxicology

Toxic if swallowed. Very toxic by inhalation. May cause severe eye irritation. Respiratory and skin irritant.

Toxicity data

(The meaning of any toxicological abbreviations which appear in this section is given here.)
IPR-RAT LDLO 15 mg kg^{-1}
IVN-RAT LD50 30 mg kg^{-1}
ORL-MUS LD50 108 mg kg^{-1}

ORL-RBT LD50 400 mg $^{-1}$
IVN-RBT LD50 36 mg kg^{-1}

Risk phrases

(The meaning of any risk phrases which appear in this section is given here.)
R25 R26 R36 R37 R38.

Transport information

(The meaning of any UN hazard codes which appear in this section is given here.)
UN No 2811. Hazard class 6.1. Packing group I.

Personal protection

Safety glasses, adequate ventilation. Do not breathe dust

[Return to Physical & Theoretical Chemistry Lab. Safety home page.]

This information was last updated on July 21, 2005. We have tried to make it as accurate and useful as possible, but can take no responsibility for its use, misuse, or accuracy. We have not verified this information, and cannot guarantee that it is up-to-date.

Chemical Toxicity and Risk Information

Chemical Name: Acetone	CAS Number:67-64-1
Synonyms: 2-Propanone, beta-Ketopropane, Dimethyl ketone, Methyl Ketone	

European Risk Category for This Chemical:

Risk Category: 2	1.Extremely Dangerous: the LD50 for rabbits exposed by the dermal route is less than 50 mg/kg body weight. 2. Very Dangerous: the LD50 in rabbits exposed by the skin route is from 25 mg/kg to 200 mg/kg body weight. 3. Dangerous: the LD50 in rabbits exposed by the dermal route is between 400 mg/kg and 2000 mg/kg body weight. 4. Other: this chemical has low toxicity or no risk information is available.

European Toxicity Risk Code for This Chemical:

Risk Code: T	TX= Very Toxic	T = Toxic
	CX = Highly Corrosive	CAN = KNown or Suspected Carcinogen
	C = Corrosive	X = Harmful
	X = Harmful	Xi = Irritant
	S = Allergen or Sensitizer	V = Low Toxicity
	n.a. = No information available	

NFPA Health Rating for this Chemical

NFPA Health: 3	0 = NONE: Materials result in injury under unusual conditions or by overwhelming dosage.
	1= SLIGHT: Short term exposure may result in minor injury that is reversible.
	2 = MODERATE: Short term exposure may result in minor temporary or permanent injury; may result in major injury.

	3 = HIGH: Short term exposure may result in major temporary or permanent injury; may threaten life.
	4 = EXTREME: Short term exposure may result in major injury or death.

NFPA Flammability Rating for this Chemical:

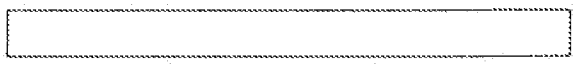
NFPA Flammability: 3	0 = NONE: Will Not Burn.
	1= MINOR: Ignites after considerable heating.
	2 = MODERATE: Ignites if moderately heated.
	3 = SEVERE: Can be ignited at all temperatures.
	4 = EXTREME: Very flammable gases or liquids.

NFPA Reactivity Rating for this Chemical:

NFPA Reactivity: 0	0 = NONE: Stable under exposure to fire. Not reactive with water.
	1= MINOR: Unstable at high temperature and pressure; may react with water with energy release, but not violently.
	2 = MODERATE: Unstable; undergoes violent chemical change, but will not detonate; may form explosive mixtures with water.
	3 = SEVERE: Explosive if initiated, heated or water added.
	4 = EXTREME: Readily explosive under normal conditions.
ACGIH Skin Notation: NO	If "YES", this chemical has been identified by the American Conference of Governmental Hygienists as one that may permeate intact skin and may cause toxic effects.:
	If "NO", this chemical has not been shown to permeate intact skin.

Other Toxicity and Risk Information

IARC Carcinogen in Animals:	If "YES", this chemical has been shown by the International Agency for Research on Cancer to cause cancer in animals. The chemical would then be a suspected Human carcinogen.
NO	If "NO", this chemical has not been shown to cause cancer in animals.
IARC Carcinogen in Humans:	If "YES", this chemical has been shown by the International Agency for Research on Cancer to have carcinogenic potential in humans.
NO	If "NO", this chemical has not been shown to be a potential carcinogen in humans.
EPA Extremely Hazardous Substance:	If "YES", this chemical appears on the list of extremely hazardous substances developed by the U.S. Environmental Protection Agency (EPA) as required by the Superfund Ammendments and the Reauthorization Act of 1986.
NO	If "NO", this chemical has not been shown to be an extreme hazard.



MATERIAL SAFETY DATA SHEET

ETHYL ALCOHOL (DENATURED)

Section I - IDENTIFICATION

PRODUCT: Ethyl alcohol (denatured)

SYNONYMS: Denatured ethanol

CHEMICAL FORMULA: C_2H_5OH

CHEMICAL ABSTRACT NO.: Mixture

PRODUCT CODE NO.: 12902

Section II - HAZARDOUS INGREDIENTS

COMPOSITION	%	CAS #	TLV	HAZARD
Ethyl alcohol	82.9	000064175	1000 ppm	Flammable
Ethyl acetate	0.2	141-78-6	400 ppm	Flammable
Methyl alcohol	16.4	000067561	200 ppm	Flammable, poisonous
Methyl ethyl ketone	0.5	000078933	200 ppm	Flammable

Section III - HEALTH & FIRST AID INFORMATION

INHALATION: Irritating to upper respiratory tract. Remove patient to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Seek medical attention immediately

INGESTION: Poisonous, may damage central nervous system and internal organs and cause blindness. DO NOT induce vomiting. Have conscious person drink several glasses of water or milk. Never give anything by mouth to an unconscious person. Lower the head so that vomit will not re-enter the mouth and throat. Seek medical attention immediately.

EYE CONTACT: Irritating, can cause colour blindness. Check for and remove any contact lenses. Rinse eyes for at least 20 minutes with cold water. Seek medical attention

Toxicity, Alcohols

Last Updated: December 13, 2005

Synonyms and related keywords: alcohol ingestion, alcohol toxicity, alcohol poisoning, ethanol poisoning, ethanol toxicity, ethanol, methanol poisoning, methanol toxicity, methanol, isopropanol toxicity, isopropanol poisoning, isopropanol, ethyl alcohol toxicity, ethyl alcohol poisoning, ethyl alcohol, methyl alcohol toxicity, methyl alcohol poisoning, methyl alcohol, isopropyl alcohol toxicity, isopropyl alcohol poisoning, isopropyl alcohol, CNS depressant, alcohol metabolism, acute alcohol intoxication

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Background: The 3 most common alcohol poisonings result from ethanol, methanol, and isopropanol (isopropyl alcohol). The devastating and potentially life-threatening toxicity that results from ingestions of any of these alcohols makes recognition of alcohol poisoning an essential part of emergency medicine.

Recognition of the morbidity and mortality that may result from ingestion of small quantities of methanol is particularly important. Ethylene toxicity is covered in a separate article (see Toxicity, Ethylene Glycol).

Pathophysiology: The organs that are most severely affected vary depending on the type of alcohol ingested.

Ethanol

Ethanol (ethyl alcohol) is an aliphatic alcohol present in aftershaves, colognes, perfumes, mouthwashes, over-the-counter (OTC) medications, and a myriad of alcoholic beverages.

Ethanol is a direct CNS depressant, which causes decreased motor function and decreased consciousness level. At high concentrations, ethanol is an anesthetic and can cause autonomic dysfunction (eg, hypothermia, hypotension), coma, and death from respiratory depression and cardiovascular collapse.

Ethanol is easily absorbed from the stomach and small intestine. When the stomach is empty, peak levels are reached 30-90 minutes after acute ingestion. When food is present in the stomach absorption is delayed. Total absorption may take as long as 6 hours.

Metabolism of ethanol is carried out in the liver by several enzymes, including alcohol dehydrogenase, aldehyde dehydrogenase, microsomal ethanol-oxidizing system (MEOS) or CYP2E1, and peroxisomal catalase. Most (90-95%) enzymes are metabolized by alcohol and aldehyde dehydrogenases. MEOS accounts for about 5% but may increase to 25% in the chronic drinker. Normally, catalase makes a small contribution to ethanol metabolism; its role is more significant at high serum ethanol concentrations.

Nonhabituated patients metabolize ethanol at 13-25 mg/dL/h. In persons with alcoholism, this rate increases to 30-50 mg/dL/h. Metabolism rates vary greatly between individuals and cannot be predicted. Similarly, because of tolerance, blood alcohol concentrations (BACs) must be interpreted in conjunction with

history and clinical presentation. Some individuals with chronic alcoholism may have an almost normal mental status and neurological examination, yet have BACs of 400 mg/dL. Conversely, nonhabituated drinkers may show marked effects of intoxication at very low BACs.

Methanol

Methanol (methyl alcohol) is found in cleaning materials, solvents, paints, varnishes, Sterno fuel, formaldehyde solutions, antifreeze, gasohol, "moonshine," windshield washer fluid (30-40% methanol), and duplicating fluids.

A CNS depressant, methanol is potentially toxic in amounts as small as a single mouthful. When metabolized by hepatic alcohol and aldehyde dehydrogenase, methanol forms formaldehyde and formic acid, both of which are toxic. The eyes, CNS, and GI tract are affected. Formic acid is the primary toxin that accounts for the majority of the anion gap, metabolic acidosis, and ocular toxicity. Lactic acid also contributes to the anion gap.

Formic acid inhibits cytochrome oxidase in the fundus of the eye. Disruption of the axoplasm is due to impaired mitochondrial function and decreased ATP production. Swelling of axons in the optic disc and edema result in visual impairment. Degradation of formic acid is folate dependent. Thus, if a folate-deficient person ingests ethanol, toxicity may be more severe due to the increased accumulation of formic acid.

Approximately 90-95% of methanol metabolism occurs in the liver, while 5-10% is excreted unchanged through the lungs and kidneys. Methanol is primarily metabolized by alcohol and aldehyde dehydrogenase. Formaldehyde has a short half-life, lasting only minutes. Formic acid is metabolized much more slowly, and it bioaccumulates with significant methanol ingestion.

Isopropanol

Isopropanol is found in OTC rubbing alcohol (70% isopropanol), antifreeze, skin lotions, and some home cleaning products.

Death from ingestion of isopropanol is uncommon. Isopropanol has 2-3 times the potency of ethanol and causes hypotension and CNS and respiratory depression more readily than ethanol. Peak levels occur approximately 30 minutes after ingestion because of rapid GI absorption, which is delayed in the presence of food. Isopropanol is a CNS and cardiac depressant with about twice the potency of ethanol. Serum levels more than 400 mg/dL are potentially fatal.

Approximately 20-50% of isopropanol is excreted unchanged by the kidney, while 50-80% is converted in the liver to acetone, which is a CNS depressant in its own right. Acetone is excreted primarily by the kidneys, with some excretion through

the lungs. The elimination half-life of isopropanol is 4-6 hours; that of acetone is 16-20 hours. The prolonged CNS depression seen with isopropanol ingestion is partially related to acetone's CNS depressant effects.

Frequency:

- **In the US:** In some studies, alcohol ingestions account for 13-14 hospital admissions per 1000 people. Ethanol is the most common alcohol ingestion. Acute intoxication is seen commonly in the ED. Other studies have shown that up to a third of all patients have detectable ethanol levels at ED presentation, irrespective of the chief complaint. Up to 72% of trauma patients had positive toxicology screen results; ethanol accounted for 55% of these findings.
- Methanol poisoning epidemics have occurred because of ingestion of contaminated "moonshine." The most notable was in Atlanta in 1951, when 90 gallons of illicit whiskey containing 35-40% methanol produced 323 poisonings and 41 deaths.
- In 1998, ethanol accounted for 33,269 exposures reported to US poison centers, of which 973 (2.9%) resulted in major toxicity and 42 (0.1%) resulted in death.
- In 1998, isopropanol accounted for 19,301 exposures reported to US poison centers, of which 83 (0.4%) resulted in major toxicity and 3 (0.02%) resulted in death.
- In 1998, methanol accounted for 1041 exposures reported to US poison centers, of which 24 (2.3%) resulted in major toxicity and 10 (1%) resulted in death.

- **Internationally:** More recently between 2002 and 2004, a total of 51 patients were admitted to the hospital in Norway with methanol poisoning, with 9 in-hospital deaths and 8 out of hospital deaths.

Mortality/Morbidity: Acute intoxication with any of these alcohols may result in coma or death due to respiratory depression and cardiovascular collapse subsequent to CNS depression.

Poor outcomes have been associated with acidosis, hypotension, or coma at presentation.

- Ethanol, when used chronically, affects multiple organ systems.

- Methanol ingestion may cause blindness.

- Isopropanol may cause severe GI hemorrhage, hemolytic anemia, and refractory hypotension.

Age: Alcohols are the most common accidental toxic ingestions by children younger than 5 years. However, because of deliberate ingestions (eg, suicide attempts, recreational use/misuse), toxic ingestions may occur at any age.

History: Humans have a long history of ingesting alcohols. Ethanol is the most common deliberate ingestion of this toxic substance. It is a component of a wide variety of beverages that are consumed nearly worldwide.

- Ethanol
  - Alcoholic beverages are the primary source of ingested ethanol. Other sources include colognes, perfumes, mouthwashes, medications, and aftershave lotions.
  - Ethanol may be ingested accidentally, as often occurs in children, or deliberately, as by the patient with alcoholism or for recreation.
  - Ethanol may be associated with other causes of altered mental status (eg, hypoglycemia, head trauma, mixed ingestions, post-ictal state, carbon dioxide narcosis, hypoxia, infection, hepatic encephalopathy). Consider these conditions when evaluating the patient with known alcohol ingestion.
- Methanol
  - Methanol ingestion may result in serious consequences, including blindness and death. A delay in treatment may lead to increased morbidity and mortality. Recognition and timely treatment are essential for a full recovery.
  - Methanol commonly is found in numerous compounds, including solvents, photocopy inks and diluents, paints, varnishes, antifreeze, gasoline mixtures (eg, gasohol, "dry gas"), canned heat (eg, Sterno), and even wines (as a byproduct of the natural fermentation process). One study of 11 patients seen between 1995 and 1997 identified 8 patients who had ingested windshield wiper fluid, one who drank gas-line antifreeze, and 2 patients with the source unknown.

- Toxicity most commonly ensues following accidental or intentional ingestion. Toxicity also may occur following inhalational exposure. Inhalation may be accidental (eg, industrial settings), or it may be deliberate (eg, volatile inhalant abuse, as in "bagging" or "huffing" solvents for their inebriant effects). Transdermal or respiratory tract absorption also may cause toxicity.

- Following ingestion, methanol is rapidly absorbed from the GI tract. Peak levels occur within 30-90 minutes of ingestion.

- Methanol is predominantly metabolized in the liver by hepatic alcohol dehydrogenase. At low serum concentrations (<20 mg/dL) and during hemodialysis, methanol elimination is quick and first-order, with an elimination half-life of about 3 hours. At higher serum concentrations, methanol elimination is slow and zero-order, at 8.5 mg/dL/h. Thus, following large doses, methanol is metabolized and eliminated very slowly. Duration of the latent period (time from ingestion until clinical toxicity is evident) is highly variable. Latent periods of 40 minutes to 72 hours have been reported; in most cases, onset of toxicity manifests in 12-24 hours. Co-ingestion of ethanol increases both the latent period (40-50 h) and elimination half-life.

- Approximately 50% of patients report visual disturbances. These disturbances usually are described as blurry, indistinct, misty, or snowstormlike. Patients also have reported yellow spots, central scotomata, and photophobia.

- CNS complaints include headache and vertigo. GI complaints may include nausea, vomiting, and abdominal pain due to direct irritation.
- Complaints do not correlate with the amount or severity of the ingestion.

- Isopropanol

  - Isopropanol is the second most commonly ingested alcohol. The most common source is rubbing alcohol (70% isopropyl alcohol). Other sources of isopropanol include window cleaners, antifreeze, detergents, jewelry cleaners, solvents, and disinfectants.

  - Ingestions typically occur in alcoholic patients, children, and those who attempt suicide. In children, exposure also may occur from inhalation or topical absorption (eg, sponge bath).

- CNS complaints include headache, dizziness, poor coordination, and confusion. GI complaints include abdominal pain, nausea, vomiting, and gastritis with hematemesis.

- Patients appear intoxicated but do not smell like ethanol; however, they may have the fruity odor of acetone.

- Obtaining a history of the substance and quantity ingested is important. The physician may need to acquire the history from emergency medical services (EMS), parents, relatives, or friends accompanying the patient. Consider other differential diagnoses for altered mental status, as more than a single cause may be present.

Physical: Alcohol ingestions may present in somewhat similar manners. An alteration in mental status is seen with all of the alcohols, given the ingestion of a sufficient quantity of the substance. This alteration may be present to varying degrees depending on the patient.

- Ethanol

  - Clinical presentation depends on BAC and tolerance to ethanol.

  - The patient may have a flushed face or diaphoresis and may be agitated or ebullient and loquacious due to early disinhibition. This condition may progress to ataxia, slurred speech, drowsiness, stupor, or coma. Nystagmus (horizontal) commonly is observed.